Is proBNP a Reliable Marker for the Evaluation of Fluid Load in Patients Undergoing Continuous Renal Replacement Therapy?

CRRT Uygulanan Hastalarda Sıvı Yükünü Değerlendirmede pro-BNP Güvenilir Bir Belirteç mi?

Overhidration and pro-BNP

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Özet

Amaç: Pro-B tipi natriüretik peptid (Pro-BNP), hemodiyaliz hastalarında volüm markerı olarak tanımlanmıştır. Bu çalışmayı yapmaktaki amacımız; overhydration nedeniyle continue renal replasman therapy (CRRT) uygulanan hastalarda, serum pro-BNP değerinin sıvı yükünü belirlemedeki rolünü değerlendirmektir. Gereç ve Yöntem: 3.düzey 7 yataklı Çocuk Yoğun Bakım Ünitesi'ne yatan, overhydration nedeniyle CRRT uygulanan hastalar çalışma çalışmaya alındı. Bulgular: Çalışma; 15'i kız (%53.6), 13'ü erkek (%46.4) toplam 28 hasta ile yapıldı. Ortalama yaşları 61.46±56.13 ay (min.2 - max.183), CRRT uygulama süresi ortalama 20.8±14.9 saat (min.5, max.60), çekilen sıvı yüzdesi ise ortalama %8.43 ± 4.51'di (min.2.5, max.20) idi. CRRT işlemi hastaların 12'sine(%42.9) sıvı yükü, 16'sına(%57.1) sıvı yükü ve eşlik eden üremi nedeniyle uygulandı. Hastaların başlangıç ve bitiş vücut ağırlığı, üre, kreatin değerleri arasında istatistiksel olarak anlamlı bir fark saptandı(p:0.001). CRRT başlamadan hemen önce bakılan ortalama proBNP 23.306 ± 13.943 pg/ml, CRRT bitiminde bakılan ortalama proBNP 22.178 ± 15.473 pg/ml bulundu. Başlangıç Pro-BNP ile bitiş Pro-BNP düzeyleri arasında anlamlı bir fark saptanmadı(p:0.756). Hastaların bitiş Pro-BNP değerleri ile bitiş vücut ağırlığı, üre, kreatin, sodyum arasında da, serum sodyum düzeyi dışında bir korelasyon yoktu(p>0.05).). Benzer şekilde başlangıç Pro-BNP değerleri ile sıvı yükü arasında (p:0.602) ve çekilen sıvı yüzdesi ile bitiş pro-BNP değerleri arasında (p:0.155) da korelasyon yoktu. Tartışma: Sıvı yükü nedeniyle CVVHDF uygulanan hastaların, sıvı yükleri ile başlangıç pro-BNP değerleri arasında ve uygulama bitiminde çekilen sıvı yüzdesi ile bitiş pro-BNP değerleri arasında ilişki saptanmadı. Biriken sıvı yükü ve çekilen sıvı miktarını değerlendirmede uygun bir belirteç olmadığı sonucuna varıldı.

Anahtar Kelimeler

Pro-BNP; Natriüretik Peptid; Sürekli Renal Replasman Tedavisi; Aşırı Sıvı Yükü

Abstract

Aim: Pro-B type natriuretic peptide (proBNP) has been defined as a volume marker in hemodialysis patients. In the present study we aimed to evaluate the role of serum proBNP levels to indicate fluid load in patients undergoing continuous renal replacement therapy (CRRT) due to overhydration. Material and Method: Patients who were admitted to a tertiary 7-bed pediatric intensive care unit and underwent CRRT due to overhydration were included in the study. Results: The study was conducted with 15 girls (53.6%) and 13 boys (46.4%). The mean age was 61.46±56.13 months (range, 2-183 months); the mean CRRT administration time was 20.8±14.9 hours (range, 5-60 hours); and the mean percentage of fluid extracted from the body was 8.43 ± 4.51% (range, 2.5-20%). CRRT was administered to 12 patients because of fluid overload (42.9%) and to 12 (57.1%) because of fluid load accompanied by uremia.. There was a statistically significant difference between body weight, urea, and creatinine levels of patients before and after treatment (p= 0.001). The mean proBNP level was 23.306 ± 13.943 pg/mL immediately before CRRT and the mean proBNP after CRRT was 22.178 ± 15.473 pg/mL. There was no statistically significant difference between the initial and final proBNP levels (p= 0.756). With the exception of serum sodium levels, there was no correlation between the final proBNP levels and body weight, urea, and creatinine (p>0.05). Similarly, there was also no correlation between initial proBNP levels and fluid load (p= 0.602) or between the percentage of extracted fluid and final proBNP levels (p= 0.155). Discussion: There was no significant correlation between the fluid load and initial proBNP levels or with the extracted fluid percentage and final proBNP levels in patients undergoing CRRT because of fluid overload.In conclusion, no appropriate marker was determined to evaluate cumulative fluid load and the extracted liquid volume.

Keywords

ProBNP; Continuous Renal Replacement Therapy; Overhydration; Natriuretic Peptide

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Introduction

B-type natriuretic peptide (BNP) levels have been frequently used for the evaluation of the prognosis and treatment outcomes of heart failure among adults. However, studies related to the use of natriuretic peptides and their particular importance among children and adolescents have recently been initiated [1, 2].

BNP is a neurohormone that consists of 32 aminoacids and is mostly synthesized from the ventricules. To a lesser extent, BNP is synthesized in the brain and the atria. Prepro-BNP, which consists of 108 aminoacids, is synthesized first and then transforms to proBNP, also with 108 aminoacids. proBNP decomposes into active BNP and N-terminal proBNP (NT-proBNP) by proteolysis. There is a pulsatile release of BNP and NT-proBNP to the circulation from myocytes with the contraction of the ventricules and

with pressure. Some BNP and NT-proBNP are released from the perimyocardial region. The half-life of BNP is approximately 20 minutes and the half-life of NT-proBNP is approximately 120 minutes. proBNP is not stored in granules as in proANP; proBNP is always released to blood during ventricular relaxation. Natriuretic peptides cause diuresis and natriuresis by increasing glomerular filtration and by decreasing sodium reabsorption in kidneys [3-5].

In 2009, Nir et al.[6] composed the broadest series to date by bringing together four studies in which NT-proBNP levels among healthy infants and children were measured using the same method. According to this series, the NT-proBNP level was very high after birth and decreased after a few days. The gradual decrease continued between the ages of 1 month and 18 years.

The aim of the study was to evaluate the role of serum proBNP levels in the identification of fluid load in patients who underwent CRRT because of overhydration.

Material and Method

Patients aged 1 month to 17 years who were admitted to the Pediatric Intensive Care Unit of Gaziantep Faculty of Medicine between June 2014 and June 2015 and who had undergone CRRT because of overhydration were included in the study. The study was approved by the local ethics committee. Age, sex, diagnosis, body weight, and period of CRRT administration, serum urea, creatinine(CRE), sodium(Na), and proBNP levels of the patients before and after CRRT were recorded. Mortality risk was calculated using the online Pediatric Index of Mortality II (PIM II) (http://www.sfar.org/scores 2/pim22.php), PRISM (Pediatric Risk of Mortality)

(http//www.sfar.org/scores 2/prism2.php) and Pediatric Logistic Organ Dysfunction (PELOD) (http://www.sfar.org/scores 2/PELOD2.php).

Serum biochemical samples were studied using a standard biochemical analyzer (Hitachi 902 Automatic Analyzer, Roche Diagnostics, Germany). ProBNP measurements were performed using the Elecsys proBNP II kit with electrochemiluminescence. The measurement range was between 5-35000 pg/mL. The most appropriate threshold value was identified as 125 pg/mL. Hemodiafiltration was performed using bicarbonated dialysate with prismaflex(Gambro, Lund,Sweden) and polysulfone membrane filters. The fluid load percentage of the patients was calculated at the beginning of the CRRT to identify the fluid balance with the formula: Percentage fluid load = (Total fluid intake in 24 hours – total fluid loss in 24 hours / patient's weight in the intensive care unit) x 100. Ultrafiltration speed (cc/kg/hour) was calculated with the following formula: amount of extracted fluid (ultrafiltration+ urine) – amount of fluid intake.

Statistical Evaluations

IBM SPSS version 22 (IBM SPSS, Turkey) was used for the statistical analyses. Conformity of the parameters to normal distribution was evaluated using the Shapiro-Wilk test. Data were analyzed using descriptive statistical methods (mean, standard deviation, and frequency) alongside the paired sample t-test for initial and final parameters that showed normal distribution, and Wilcoxon's signed-rank test for evaluating parameters without normal distribution. Spearman's Rho test was used to calculate relations between the parameters. Significance was considered as $p<0.05$.

Results

A total of 28 patients, 15 girls (53.6%) and 13 boys (46.4%) who were administered CRRT between June 2014 and June 2015 were included in the study. The mean age was 61.46±56.13 months (range, 2-183 months), and mean body weight was 17.27±11.99 kg (range, 5-64 kg). Twelve patients (42.9%) were monitored because of chronic renal disease. Fluid overload was observed in all patients who were administered CRRT (range, 2.5-25%, mean 11.23±6.88%).

The mean CRRT administration period was 20.8±14.9 hours (range, 5-60 hours), and the mean percentage of extracted fluid was 8.43±4.51% (range, 2.5-20%). Anticoagulation was used in 18 (64.3%) administrations. CRRT was administered to 12 patients (42.9%) because of fluid overload and to16 (57.1) patients because of fluid overload and uremia. The patients' mean PIM score was found to be 34.64±17.91 and the mean

PRISM score was 21.30±9.04. The mean PELOD score was measured as 21.36±7.55.

There was a statistically significant difference between body weight, urea, and creatinine levels of the patients before and after CRRT (p= 0.001); however, no significant difference was detected between the initial and final proBNP levels (p= 0.756) (Table 1).

There was no correlation between initial proBNP levels and urea, creatinine, body weight, and Na levels (p>0.05) (Table 2). With the exception of serum sodium levels, there was no correlation between final proBNP levels and final body weight, urea,

Table 1. Comparison of patients initial and final parameters

	Initial Mean±SS (Median)	Final Mean±SS (Median)	P
Body weight(kg)	18.22±12.01	17.14±11.94	[1]0.001**
Urea(mg/dL)	140.86±84.07	55.79±34.68	[1]0.001**
Na(mmol/L)	138.46±8.43	137.07±5.35	[1]0.365
proBNP(pg/mL)	23306.21±13943.95 (34500)	22178.07±15473.68 (34000)	[2]0.756
Cre(mg/dL)	2.91±3.11 (1.35)	1.21±1.65 (0.65)	[2]0.001**

[1]Paired sample t-test [2]Wilcoxon signed-rank test **p<0.01

Table 2. Evaluation of correlations between initial proBNP levels and other parameters

	Initial proBNP
	r
Fluid load	-0.103
Initial body weight	0.039
Initial urea	0.151
Initial CRE	0.186
Initial Na	0.204

Spearman's Rho Test

and creatinine (p>0.05). There was a statistically significant relation between final proBNP and final Na levels at 37.9% (r= 0.379, p= 0.049) (Table 3).

Table 3. Evaluation of correlations between final proBNP levels and other parameters

	Final proBNP
	r
Extracted fluid (%)	0.281
Final body weight	0.016
Final urea	0.139
Final Cre	0.261
Final Na	0.379

Spearman's Rho Test *p<0.05

The mean proBNP measured just before CRRT was 23.306±13.943 pg/mL and the mean proBNP after CRRT was 22.178±15.473 pg/mL. There was no statistically significant difference between the initial and final proBNP levels (p= 0.756). Similarly, there was no correlation between initial proBNP levels and fluid load (p= 0.602), and no correlation was identified between the extracted fluid percentage and final proBNP levels (p= 0.155).

Discussion

The reported non-invasive methods used to identify the blood volume in circulation are measuring the diameter of the inferior vena cava (IVC) and the diameter of the left atrium using bioimpedance spectroscopy [7]. Although there is a consensus that NT-proBNP is a constant marker of ventricular dysfunction, it is hard to say that there is a direct relation between NT-proBNP levels and volume load because of the differences between the results of the studies.

In 2008, Bargnoux et al.[8] identified 39%, 59%, and 36% decreased levels of BNP, NT-proBNP, and proBNP, respectively, compared with baseline after dialysis in 31 hemodialysis patients. However, they also indicated that the decrease was not correlated with the decrease in the extracted fluid and body weight. Although there was no significant difference between the body weights before and after dialysis in our study, we observed no significant differences between the proBNP levels.

In an article published in 2014, there were significant decreases in the rates of overhydration/extracellular fluid and systolic and diastolic blood pressure (SBP and DBP) and on the NT-proBNP level after hemodialysis. Pre- and post-HD, SBP, DBP, LVMI (left ventricular mass index), and NT-proBNP levels were higher in overhydrated patients compared with patients who were not overhydrated [9].

Leowattana et al.[10] indicated that NT-proBNP levels were higher among chronic hemodialysis patients and emphasized that a specific cut-off value must be determined for these patients.

Anderson et al. [11] reported that higher levels of ANP and NT-proBNP were found among 20 patients with nephrotic syndrome during an attack compared with the remission group.

In a study conducted with 94 hemodialysis patients by Racek et al.[12] both BNP and NT-proBNP were reported to be high; after hemodialysis there was a significant decrease in BNP levels, whereas there was a significant increase in NT-proBNP. The authors reported that the changes that developed in both peptides during hemodialysis were due to the membrane type of the dialysis filter. In our study, we used the same type of filter and hemodialyis module for all patients.

Many studies have been conducted to identify the role of serum BNP levels in the prognosis of adult patients who undergo hemodialysis. Sun et al.[13] reported in their 2-year study of 217 patients that BNP and NT-proBNP had higher sensitivity and specificity for cardiovascular events, and that NT-proBNP was a better marker than BNP for mortality. In their multicentered study with 753 patients, Paniagua et al.[14] concluded that NT-proBNP was a good marker for mortality, independent of fluid load and dialysis modality. The authors stated that NT-proBNP was a good marker for prognosis because its half-life was longer and provided more accurate results as an index of ventricular stress. In a similar way, Naganuma reported that for determining the risk of cardiac death in patients undergoing hemodialysis, high level plasma concentration of BNP was a useful parameter independent of factors, such as left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), age, serum albumin, and C-reactive protein (CRP) [15]. In another study conducted in 2002, the level of BNP was determined as the only independent marker of sudden death after 3 years of follow-up of 452 patients with EF 35% and below [16]. We did not investigate the relation between proBNP level and mortality in our study.

Sheen et al.[17] reported no correlation between intradialitic BNP levels and body weight, median systolic blood pressure, and median diastolic blood pressure, but that patients with systolic dysfunction had the highest BNP values. In another study in which indicators of volume were analyzed using bioelectronic impedance, inferior vena cava ultrasound, and serum NT-proBNP levels, outcomes were not related to the fluid volume [18]. Another study conducted in 2003 reported that BNP levels had limited value for the evaluation of overhydration in HD patients [19].

Lee et al.[20] investigated NT-proBNP level, extracellular fluid (ECW%), and left ventricular dysfunction in patients who had undergone continuous ambulatory peritoneum dialysis (CAPD). The authors reported that they found no relation between serum NT-proBNP concentration with ECW%, and that NT-proBNP was not a good marker to determine fluid levels in patients undergoing CAPD, but that it could be used to evaluate for LV hypertrophy and LV dysfunction. They suggested that the increase in NT-proBNP in patients undergoing CAPD might be due to a response to chronic stimulation as a consequence of increased cardiomyocyte contraction and not solely as a conse-

quence of increased extracellular fluid. Indeed, Lang et al.[21] identified that the loading of IV saline resulted in an increase in ANP levels but that the increase in BNP was not significant. There was no significant relation between the fluid loads and initial proBNP levels or between the percentage of the extracted fluid load and final proBNP levels in patients who had undergone CRRT because of fluid overload. As a consequence, proBNP was not considered to be an appropriate marker for the evaluation of accumulated fluid load or the volume of extracted fluid. Different markers are required for the evaluation of fluid load in critical pediatric patients.

Competing interests

The authors declare that they have no competing interests.

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